Genetic modifiers of CHEK2*1100delC associated breast cancer risk

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CONFLICT OF INTEREST NOTIFICATION PAGE

CONFLICT OF INTEREST: The authors declare no conflict of interest. The funders had no role in conception and design of the study, nor in interpretation of the final results.

FUNDING

The Breast Cancer Association Consortium (BCAC) is funded by Cancer Research UK [C1287/A10118, C1287/A12014] and by the European Community´s Seventh Framework Programme under grant agreement number 223175 (grant number HEALTH-F2-2009-223175) (COGS).

Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund.

The Australian Breast Cancer Family Study (ABCFS) was supported by grant UM1 CA164920 from the National Cancer Institute (USA). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia) and the Victorian Breast Cancer Research Consortium. JLH is a National Health and Medical Research Council (NHMRC)

Australia Fellow and a Victorian Breast Cancer Research Consortium Group Leader. MCS is a NHMRC Senior Research Fellow and a Victorian Breast Cancer Research Consortium Group Leader.

The Amsterdam Breast Cancer Study (ABCS) was supported by the Dutch Cancer Society [grants NKI 2007-3839; 2009 4363]; BBMRI-NL, which is a Research Infrastructure financed by the Dutch government (NWO 184.021.007); and the Dutch National Genomics Initiative.

The work of the Bavarian Breast Cancer Cases and Controls (BBCC) was partly funded by ELAN-Fond of the University Hospital of Erlangen.

The British Breast Cancer Study (BBCS) is funded by Cancer Research UK and Breakthrough Breast Cancer and acknowledges NHS funding to the NIHR Biomedical Research Centre, and the National Cancer Research Network (NCRN).

EJS is supported by NIHR Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London, United Kingdom. IT is supported by the Oxford Biomedical Research Centre.

The Breast Cancer Study of the University of Heidelberg (BSUCH) was supported by the Dietmar-Hopp Foundation, the Helmholtz Society and the German Cancer Research Center (DKFZ).

The Copenhagen General Population Study (CGPS) was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council and Herlev Hospital.

The ESTHER Breast Cancer Study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe).

The German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) is supported by the German Cancer Aid (grant no 110837, coordinator: RKS).

The Gene Environment Interaction and Breast Cancer in Germany (GENICA) was funded by the Federal Ministry of Education and Research (BMBF) Germany grants 01KW9975/5, 01KW9976/8,

01KW9977/0 and 01KW0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany.

The Genetic Epidemiology Study of Breast Cancer by Age 50 (GESBC) was supported by the Deutsche Krebshilfe e. V. [70492] and the German Cancer Research Center (DKFZ).

The Hannover Breast Cancer Study (HABCS) study was supported by the Rudolf Bartling Foundation.

The Helsinki Breast Cancer Study (HEBCS) was financially supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (266528), the Finnish Cancer Society, The Nordic Cancer Union and the Sigrid Juselius Foundation. The work of TAM has been supported by Ida Montin Foundation, Cancer Society of Finland and Finnish Cultural Foundation.

The Hannover-Minsk Breast Cancer Study (HMBCS) was supported by a grant from the Friends of Hannover Medical School and by the Rudolf Bartling Foundation.

The Hannover-Ufa Breast Cancer Study (HUBCS) was supported by a grant from the German Federal Ministry of Research and Education (RUS08/017).

"Financial support for the Karolinska Breast Cancer Study (KARBAC) was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Cancer Society, The Gustav V Jubilee foundation and and Bert von Kantzows foundation.

The Kuopio Breast Cancer Project (KBCP) was financially supported by the special Government Funding (EVO) of Kuopio University Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, and by the strategic funding of the University of Eastern Finland.

The Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer (kConFab) is supported by a grant from the National Breast Cancer Foundation, and previously by the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia.

Financial support for the Australian Ovarian Cancer Study (AOCS) was provided by the United States Army Medical Research and Materiel Command [DAMD17-01-1-0729], Cancer Council Victoria, Queensland Cancer Fund, Cancer Council New South Wales, Cancer Council South Australia, The Cancer Foundation of Western Australia, Cancer Council Tasmania and the National Health and Medical Research Council of Australia (NHMRC; 400413, 400281, 199600).

The Leuven Multidisciplinary Breast Centre (LMBC) is supported by the 'Stichting tegen Kanker' (232-2008 and 196-2010). DL is supported by the FWO and the KULPFV/10/016-SymBioSysII.

The Mayo Clinic Breast Cancer Study (MCBCS) was supported by the NIH grants CA128978, CA116167, CA176785 an NIH Specialized Program of Research Excellence (SPORE) in Breast Cancer [CA116201], and the Breast Cancer Research Foundation and a generous gift from the David F. and Margaret T. Grohne Family Foundation and the Ting Tsung and Wei Fong Chao Foundation.

The Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 209057, 251553 and 504711 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry (VCR) and the Australian Institute of Health and Welfare (AIHW), including the National Death Index (NDI) and the Australian Cancer Database.

The Norwegian Breast Cancer Study (NBCS) has received funding from the K.G. Jebsen Centre for Breast Cancer Research; the Research Council of Norway grant 193387/V50 (to ALBD and VKr) and

grant 193387/H10 (to ALBD and VKr), South Eastern Norway Health Authority (grant 39346 to to ALBD and VKr) and the Norwegian Cancer Society (to to ALBD and VKr).

The Northern California Breast Cancer Family Registry (NC-BCFR) was supported by grant UM1 CA164920 from the National Cancer Institute (USA). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR.

The Ontario Familial Breast Cancer Registry (OFBCR) was supported by grant UM1 CA164920 from the National Cancer Institute (USA). The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the USA Government or the BCFR.

The Leiden University Medical Centre Breast Cancer Study (ORIGO) was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16).

The NCI Polish Breast Cancer Study (PBCS) was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA.

The Rotterdam Breast Cancer Study (RBCS) was funded by the Dutch Cancer Society (DDHK 2004-3124, DDHK 2009-4318).

The Singapore and Sweden Breast Cancer Study (SASBAC) was supported by funding from the Agency for Science, Technology and Research of Singapore (A*STAR), the US National Institute of Health (NIH) and the Susan G. Komen Breast Cancer Foundation.

The Sheffield Breast Cancer Study (SBCS) was supported by Yorkshire Cancer Research S295, S299, S305PA and Sheffield Experimental Cancer Medicine Centre.

The Study of Epidemiology and Risk factors in Cancer Heredity (SEARCH) is funded by a programme grant from Cancer Research UK [C490/A10124] and supported by the UK National Institute for Health Research Biomedical Research Centre at the University of Cambridge.

The UCI Breast Cancer Study (UCIBCS) component of this research was supported by the NIH [CA58860, CA92044] and the Lon V Smith Foundation [LVS39420].

The UK Breakthrough Generations Study (UKBGS) is funded by Breast Cancer Now and the Institute of Cancer Research (ICR), London. ICR acknowledges NHS funding to the NIHR Biomedical Research Centre

ABSTRACT

Purpose

*CHEK2**1100delC is a founder variant in European populations conferring a 2-3 fold increased risk of breast cancer (BC). Epidemiologic and family studies have suggested that the risk associated with *CHEK2**1100delC is modified by other genetic factors in a multiplicative fashion. We have investigated this empirically using data from the Breast Cancer Association Consortium (BCAC).

Methods

With genotype data of 39,139 (624 1100delC carriers) BC patients and 40,063 (224) healthy controls from 32 BCAC studies, we analyzed the combined risk effects of *CHEK2**1100delC and 77 common variants in terms of a polygenic risk score (PRS) and pairwise interaction.

Results

The PRS conferred an odds ratio (OR) of 1.59 [95% CI 1.21-2.09] per standard deviation for BC for *CHEK2**1100delC carriers and 1.58 [1.55-1.62] for non-carriers. No evidence for deviation from the multiplicative model was found. The OR for the highest quintile of the PRS was 2.03 [0.86-4.78] for *CHEK2**1100delC carriers placing them to the high risk category according to UK NICE guidelines. OR for the lowest quintile was 0.52 [0.16-1.74], indicating life-time risk close to population average.

Conclusion

Our results confirm the multiplicative nature of risk effects conferred by *CHEK2**1100delC and the common susceptibility variants. Furthermore, the PRS could identify the carriers at a high life-time risk for clinical actions.

Keywords: Breast cancer; *CHEK2**1100delC; Polygenic risk score (PRS); common variants; Breast Cancer Association Consortium (BCAC)

INTRODUCTION

The protein truncating mutation *CHEK2**1100delC (checkpoint kinase 2) is a moderate penetrance breast cancer risk variant with relative risk estimate of 2-3 fold.[1, 2] However, several studies have shown that the cumulative life-time risk of breast cancer in *CHEK2**1100delC carriers is markedly higher in women with a family history than without,[3-5] and that *CHEK2**1100delC carriers have a higher probability of developing bilateral breast cancer.[6] These observations are quantitatively consistent with a simple polygenic model suggesting that *CHEK2**1100delC combines multiplicatively with other genetic loci. However, this has not yet been established empirically.

Genome wide association studies have identified common genetic variants that are associated with increased risk of breast cancer. A polygenic risk score (PRS), based on 77 low penetrance variants has been estimated to explain approximately 12-14% of the excess familial risk and shown to identify individuals at high risk at the population level.[7, 8] Some of these variants predominantly predispose to either estrogen receptor positive (ER+) or estrogen receptor negative (ER-) disease, which represent the two main etiological subclasses of breast cancer.[9] *CHEK2**1100delC carriers are more strongly predisposed to ER+ disease: about 90% of carrier tumors are ER+ in comparison to 77-78% of non-carrier tumours.[10]

Here, we investigate the synergistic risk effects attributable to *CHEK2**1100delC and the common breast cancer susceptibility variants both individually and summarized in terms of the PRS.[7, 8]

PATIENTS AND METHODS

Study participants

Female invasive breast cancer patients and healthy controls of European ancestry were included from studies participating in the Breast Cancer Association Consortium (BCAC)(Table S1). Data from a study were included if the study provided genotype data of the common variants from at least one breast cancer patient carrying the 1100delC variant. This selection yielded data from 32 studies and

a total of 79,202 study subjects, including 848 *CHEK2**1100delC carriers (Table S2) for pairwise interaction analyses. Complete quality controlled[7, 10] genotype data for all common variants and *CHEK2**1100delC were available from 33,624 study subjects (369 *CHEK2**1100delC carriers, Table S2). This data were used in the analyses involving the PRS.

All participating studies were approved by their institutional review committees. Each study followed national guidelines for participant inclusion and informed consent procedures.

Genotyping

All variants except *CHEK2**1100delC were genotyped centrally using a custom Illumina iSelect genotyping array (iCOGS, Illumina, Inc. San Diego, CA, USA) as part of the COGS consortium studies as described earlier.[7, 8] *CHEK2**1100delC was primarily genotyped using a custom made TaqMan assay (Applied Biosystems, Foster City, CA, USA), with a small minority being genotyped using iPLEX.[10] In addition to the 38,549 study subjects genotyped using the iCOGS array, 40,653 BCAC study subjects were genotyped for up to 25 of the common risk variants and these data were used in the pairwise interaction analysis (Table S2, Table S3). These samples were genotyped by independent studies following BCAC genotyping standards as described previously.[11, 12]

Statistical analyses

Statistical analyses were performed using Stata SE 10 (StataCorp, Texas, USA) and R version 2.15.2.[13] For the common variants a log-additive model was assumed; i.e. the risk was analyzed in terms of the number of disease-associated alleles [0,1,2] carried. *CHEK2**1100delC was assumed to follow a dominant inheritance model as the number of rare homozygotes was small (n=19). All analyses were adjusted for study and seven principal components defined on the basis of the genome-wide data from the iCOGS project as described previously.[7] All reported tests were two-sided.

Polygenic risk score

In order to investigate the combined effects of common variants and *CHEK2**1100delC, a polygenic risk score (PRS) based on the main effects of the common variants was calculated using the formula:

$$\sum_{i=1}^{n} a_i \log_2 OR_i$$

where n is the number of loci included in the model, a is the number of susceptibility alleles in locus i and OR is the per allele odds ratio for breast cancer, estimated separately for each variant in the whole data set (Table S4a, column "All"). Results using a PRS based on previously reported ORs[7, 8] were essentially identical (data not shown). The PRS was approximately normally distributed in all study subgroups, and was standardized by mean and standard deviation of the PRS among the healthy individuals.[8] For pairs of linked variants with r2>0.75, we included in the PRS only the lead variant (rs2981579, not rs2981582; rs12662670, not rs3757318; rs554219, not rs614367). We excluded two variants (rs78540526 and rs75915166) included in the PRS of Mavaddat et al.[8], which were not genotyped on the iCOGS array, as well as rs17879961, the *CHEK2* missense variant I157T, because the number of study subjects carrying both 1100delC and I157T was very low (n=5). Thus, the resulting PRS included 74 variants. The interaction between PRS and *CHEK2**1100delC was assessed by comparing nested logistic regression models: a model including the PRS and 1100delC genotype and a model supplemented with an interaction term, coded as the product of the PRS and 1100delC. In analyses of the PRS and positive family history of breast cancer, positive family history was defined as at least one first degree relative with breast cancer.

The cumulative life-time breast cancer risk of *CHEK2**1100delC carriers in different PRS-percentiles was derived assuming an average life-time risk of 22% for CHEK2*1100delC carriers[14] and previously published relative risk estimates associated with the PRS.[8]

Pairwise interaction analyses

We tested for pairwise interaction between each common variant and *CHEK2**1100delC as described above for the interaction between the PRS and 1100delC. P-values were corrected for 77 parallel tests using the Benjamini-Hochberg method.[15] The OR for breast cancer was estimated

separately for each of the common variants for the whole dataset and for the subgroup of 1100delC carriers. These analyses were also performed separately on a subgroup of breast cancer patients with ER+ disease, because 1100delC is associated with ER+ breast cancer.[10] We tested for heterogeneity in the ORs among different BCAC studies by including an interaction term between variant and the study, separately for each variant. No significant heterogeneity was found for any variant (data not shown). Statistical power was estimated as previously suggested for risk interaction analyses.[16]

RESULTS

We analyzed the combined effects of *CHEK2**1100delC and common low penetrance breast cancer risk variants using data from the international Breast Cancer Association Consortium (Table S2). The PRS summarizing the individual effects of 74 common variants was strongly associated with breast cancer risk among *CHEK2**1100delC carriers (OR per unit standard deviation 1.59 [1.21-2.09], P=0.0008) and the OR was similar to that in non-carriers (1.58 [1.55-1.62], $P_{interaction}$ 0.93). ORs for the highest and lowest quintiles of the PRS distribution were 2.03 [0.86-4.78] and 0.52 [0.16-1.74] for *CHEK2**1100delC carriers, respectively, when compared to the middle quintile (Table 1). Both estimates were similar to those among non-carriers.

The OR associated with *CHEK2**1100delC in the analysis data set 2.99 [2.32–3.85] was attenuated, when the model was adjusted for positive family history of breast cancer. The OR associated with the PRS was also slightly attenuated (Table 2). No significant interaction between risk effects associated with 1100delC, PRS and positive family history was found. However, in a case-only analysis there was a significant association between the PRS and family history of breast cancer, among both *CHEK2**1100delC carriers (OR 1.29 [1.01-1.65], P=0.04) and non-carriers (OR 1.17 [1.12-1.21], P=4E-16) (Figure S1).

When altogether 77 common variants were considered individually, we found nominally significant interactions between five variants and *CHEK2**1100delC for overall breast cancer (rs11249433,

rs11780156, rs204247, rs2981582 and rs704010; Table S4a). Two of these represented synergistic (more than multiplicative) and three antagonistic interactions (the estimated effect in 1100delC carriers being in the opposite direction to that in non-carriers). However, none of the interactions were significant after correction for multiple testing. Nine variants showed a nominally significant interaction for ER-positive breast cancer (Table S4b).

DISCUSSION

Our analyses on the synergistic effects of *CHEK2**1100delC and 77 common low penetrance variants on breast cancer risk give strong support to the predicted multiplicative polygenic model.[8, 17, 18] While this has previously been shown for combinations of low penetrance variants,[8] and for variants in combination with BRCA1 and BRCA2 mutations,[19] this is the first direct demonstration for a "moderate" risk gene and has important implications for risk prediction. The PRS was a significant risk factor for *CHEK2**1100delC carriers, and the estimated OR per unit standard deviation was very similar in *CHEK2**1100delC carriers and in non-carriers, consistent with the hypothesis that the common susceptibility variants combine with the rare *CHEK2**1100delC variant in an approximately multiplicative fashion. Similarly, the PRS risk estimates for the highest and lowest quintiles did not differ between the *CHEK2**1100delC carriers and non-carriers. These two estimates in the *CHEK2**1100delC carriers alone did not reach statistical significance (Table 1), possibly reflecting limited statistical power due to the relatively low number of healthy variant carriers (Table S2). However, this is the largest study genotyped for *CHEK2**1100delC and these common variants, and even though some of the point estimates are not significant, they are consistent with the previous reports. Most importantly, we did not find evidence for deviation from the multiplicative model, suggesting that the PRS could be used in risk stratification of 1100delC carriers in a similar manner to non-carriers.

The unadjusted OR for the *CHEK2**110delC variants (Table 2) was higher in our analysis data set than in previous reports.[2, 14] Adjusting for positive family history markedly attenuated the

*CHEK2**1100delC associated OR, suggestive of some oversampling of familial cases. The PRS OR was also slightly attenuated after the adjustment. However, *CHEK2**1100delC, PRS and family history remained significant risk factors in the combined model (Table 2) suggesting that the common variants together explain part of the excess familial risk as previously suggested,[17] but that the PRS has predictive value also in breast cancer families segregating *CHEK2**1100delC.

Recently, a large study estimating the risk associated with *CHEK2**1100delC in relation to age, tumor subtype and family history reported the cumulative life-time risk for 1100delC carriers to be about 22%.[14] Assuming that the relative effect of the PRS is the same in carriers and non-carriers (OR higher than 1.48 [1.39-1.57] or lower than 0.65 [0.60–0.70] for percentiles above 80% or lower than 20%, respectively),[8] 20% of the 1100delC carriers with highest PRS would have life-time risk higher than 32.6% [30.6%-34.5%] exceeding the threshold for the high-risk category (>30%) according to the UK NICE guidelines for familial breast cancer.[20] Similarly, for the 20% of 1100delC carriers with lowest PRS, the life-time risk would be lower than 14.3% [13.2%-15.4%], i.e. close to the average population risk. These observations imply that, if *CHEK2**1100delC is to be used in risk prediction, it can be made more effective by including the PRS, representing the risk modifying effects of common variants, in the prediction.

*CHEK2**1100delC carrier cancers do not represent a phenotypically distinct subgroup of breast carcinomas. Instead, the phenotypic diversity of *CHEK2**1100delC associated cancers resembles that of breast tumors in general.[10] Thus, it was not surprising that the relative risks conferred by the common variants were similar for the *CHEK2**1100delC carriers and for non-carriers, and no significant pairwise interaction was found. We estimated that we had sufficient statistical power (80%, at $P<0.05$) to detect a pairwise interaction between *CHEK2**1100delC and any of the common variants, if the interaction OR was 2.5 or greater, but not enough power to detect interactions comparable in magnitude to the risk effects associated with the low penetrance variants (OR 1.1-1.5). Thus, it remains possible that more modest departures from a multiplicative model may exist. If so,

however, much larger case-control studies, perhaps combined with pedigree analyses, will be required to detect them.

In conclusion, our analyses confirm the predicted multiplicative relationship between *CHEK2**1100delC and the common low penetrance variants. Hence, the PRS could be similarly applied for risk prediction for the variant carriers as for the general population. Most importantly, the PRS could help identifying the high risk group of the *CHEK2**1100delC carriers, who would best benefit from clinical intervention.

ACKNOWLEDGEMENTS

We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians and administrative staff who enabled this work to be carried out (details in online Supplementary data).

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LEGENDS TO FIGURES AND TABLES

Table 1. Breast cancer risk associated with the polygenic risk score (PRS) for non-carriers and the carriers of *CHEK2**1100delC.

Table 2. Relative breast cancer risk associated with *CHEK2**1100delC, PRS and positive family history of breast cancer in the analysis data set.

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Supplementary data. Detailed acknowledgement

SUPPLEMENTARY DATA: DETAILED ACKNOWLEDGEMENTS

We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians and administrative staff who have enabled this work to be carried out. Especially we thank the staffs of the Centre for Genetic Epidemiology Laboratory, the CNIO genotyping unit, the McGill University and Génome Québec Innovation Center, the Copenhagen DNA laboratory and the Mayo Clinic Genotyping Core Facility; Maggie Angelakos, Judi Maskiell, Gillian Dite (ABCFS); Sten Cornelissen, Richard van Hien, Linde Braaf, Annegien Broeks, Emiel Rutgers, C Ellen van der Schoot, Femke Atsma (ABCS); Eileen Williams, Elaine Ryder-Mills, Kara Sargus (BBCS); Niall McInerney, Gabrielle Colleran, Andrew Rowan, Angela Jones (BIGGS); Peter Bugert, Medical Faculty Mannheim (BSUCH); Staff and participants of the Copenhagen General Population Study. For the excellent technical assistance: Dorthe Uldall Andersen, Maria Birna Arnadottir, Anne Bank, Dorthe Kjeldgård Hansen (CGPS); Hartwig Ziegler, Sonja Wolf, Volker Hermann, Christa Stegmaier, Katja Butterbach (ESTHER); Stefanie Engert, Heide Hellebrand, Sandra Kröber (GC-HBOC); The GENICA Network: Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany [HB, Wing-Yee Lo, Christina Justenhoven], German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ) [HB], Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany [Yon-Dschun Ko, Christian Baisch], Institute of Pathology, University of Bonn, Germany [Hans-Peter Fischer], Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany [UH], Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany [Thomas Brüning, Beate Pesch, Sylvia Rabstein, Anne Lotz]; and Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany [Volker Harth]; Ursula Eilber (GESBC); Michael Bremer (HABCS); Kirsimari Aaltonen, Karl von Smitten, Tuomas Heikkinen, Irja Erkkilä (HEBCS); Peter Hillemanns, Hans Christiansen and Johann H. Karstens (HMBCS); Eija Myöhänen, Helena Kemiläinen (KBCP); Heather

Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow Up Study (which has received funding from the NHMRC, the National Breast Cancer Foundation, Cancer Australia, and the National Institute of Health (USA)) for their contributions to this resource, and the many families who contribute to kConFab (kConFab/AOCS); Gilian Peuteman, Dominiek Smeets, Thomas Van Brussel and Kathleen Corthouts (LMBC); Dr. Kristine Kleivi, PhD (K.G. Jebsen Centre for Breast Cancer Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway and Department of Research, Vestre Viken, Drammen, Norway), Dr. Lars Ottestad, MD (Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Oslo, Norway), Prof. Em. Rolf Kåresen, MD (Department of Oncology, Oslo University Hospital and Faculty of Medicine, University of Oslo, Oslo, Norway), Dr. Anita Langerød, PhD (Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Oslo, Norway), Dr. Ellen Schlichting, MD (Department for Breast and Endocrine Surgery, Oslo University Hospital Ullevaal, Oslo, Norway), Dr. Marit Muri Holmen, MD (Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway), Prof. Toril Sauer, MD (Department of Pathology at Akershus University hospital, Lørenskog, Norway), Dr. Vilde Haakensen, MD (Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Oslo, Norway), Dr. Olav Engebråten, MD (Institute for Clinical Medicine, Faculty of Medicine, University of Oslo and Department of Oncology, Oslo University Hospital, Oslo, Norway), Prof. Bjørn Naume, MD (Division of Cancer Medicine and Radiotherapy, Department of Oncology, Oslo University Hospital Radiumhospitalet, Oslo, Norway), Dr. Cecile E. Kiserud, MD (National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital, Oslo, Norway and Department of Oncology, Oslo University Hospital, Oslo, Norway), Dr. Kristin V. Reinertsen, MD (National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital, Oslo, Norway and Department of Oncology, Oslo University Hospital, Oslo, Norway), Assoc. Prof. Åslaug Helland, MD (Department of Genetics, Institute for Cancer Research and Department of Oncology, Oslo University Hospital

Radiumhospitalet, Oslo, Norway), Dr. Margit Riis, MD (Dept of Breast- and Endocrine Surgery, Oslo University Hospital, Ullevål, Oslo, Norway), Dr. Ida Bukholm, MD (Department of Breast-Endocrine Surgery, Akershus University Hospital, Oslo, Norway and Department of Oncology, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital, Oslo, Norway), Prof. Per Eystein Lønning, MD (Section of Oncology, Institute of Medicine, University of Bergen and Department of Oncology, Haukeland University Hospital, Bergen, Norway), Dr Silje Nord, PhD (Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Oslo, Norway) and Grethe I. Grenaker Alnæs, M.Sc. (Department of Genetics, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Oslo, Norway) (NBCS); Teresa Selander, Nayana Weerasooriya (OFBCR); E. Krol-Warmerdam, and J. Blom for patient accrual, administering questionnaires, and managing clinical information. The LUMC survival data were retrieved from the Leiden hospital-based cancer registry system (ONCDOC) with the help of Dr. J. Molenaar (ORIGO); Louise Brinton, Mark Sherman, Neonila Szeszenia-Dabrowska, Beata Peplonska, Witold Zatonski, Pei Chao, Michael Stagner (PBCS); Petra Bos, Jannet Blom, Ellen Crepin, Elisabeth Huijskens, Annette Heemskerk, the Erasmus MC Family Cancer Clinic (RBCS); The Swedish Medical Research Counsel (SASBAC); Sue Higham, Helen Cramp, Ian Brock, Sabapathy Balasubramanian and Dan Connley (SBCS); The SEARCH and EPIC teams (SEARCH); Irene Masunaka (UCIBCS); Breast Cancer Now and the Institute of Cancer Research for support and funding of the Breakthrough Generations Study, and the study participants, study staff, and the doctors, nurses and other health care providers and health information sources who have contributed to the study. We acknowledge NHS funding to the Royal Marsden/ICR NIHR Biomedical Research Centre (UKBGS).

The iCOGS study would not have been possible without the contributions of the following: Andrew Berchuck (OCAC), Rosalind A. Eeles, Ali Amin Al Olama, Zsofia Kote-Jarai, Sara Benlloch (PRACTICAL), Georgia Chenevix-Trench, Antonis Antoniou, Lesley McGuffog and Ken Offit (CIMBA), Andrew Lee, and Ed Dicks, Craig Luccarini and the staff of the Centre for Genetic Epidemiology Laboratory, Javier Benitez, Anna Gonzalez-Neira and the staff of the CNIO genotyping unit, Jacques Simard and Daniel C.

Tessier, Francois Bacot, Daniel Vincent, Sylvie LaBoissière and Frederic Robidoux and the staff of the McGill University and Génome Québec Innovation Centre, the staff of the Copenhagen DNA laboratory, and Julie M. Cunningham, Sharon A. Windebank, Christopher A. Hilker, Jeffrey Meyer and the staff of Mayo Clinic Genotyping Core Facility

Table 1. Breast cancer risk associated with the polygenic risk score (PRS) for non-carriers and the carriers of CHEK2*1100delC.

	Non-carriers		CHEK2*1100delC carriers	
	OR [95% CI]	**P**	**OR [95% CI]**	**P**
PRS[a]	1.58 [1.55 - 1.62]	<1.0E-10	1.59 [1.21 - 2.09][b]	0.0008
Percentile of PRS, %				
< 20	0.52 [0.48 - 0.56]	<1.0E-10	0.52 [0.16 - 1.74]	0.29
20-40	0.78 [0.72 - 0.84]	2E-11	0.72 [0.28 - 1.88]	0.51
40-60	referent		referent	
60-80	1.25 [1.16 - 1.34]	8E-10	0.93 [0.39 - 2.25]	0.88
> 80	1.92 [1.80 - 2.06]	<1.0E-10	2.03 [0.86 - 4.78]	0.11

[a] Odds ratio (OR) was estimated per unit standard deviation of the PRS.

[b] P-value for pairwise interaction between CHEK2*1100delC and PRS: 0.93.

Table 2. Relative breast cancer risk associated with CHEK2*1100delC, PRS and positive family history of breast cancer in the analysis data set.

Risk model	Parameters	OR	[95% CI]	P
BC ~ 1100delC + PRS	1100delC	2.99	[2.32 - 3.85]	<1.0E-10
	PRS	1.58	[1.55 - 1.62]	<1.0E-10
BC ~ 1100delC + PRS + family history	1100delC	2.42	[1.71 - 3.47]	9.4E-7
	PRS	1.55	[1.50 - 1.60]	<1.0E-10
	family history[a]	2.73	[2.48 - 3.47]	<1.0E-10

a No significant interaction between positive family history of breast cancer and either *CHEK2*1100delC* or PRS was found.

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Table S1. Description of study design and genotype data availability of 32 studies participating in the Breast Cancer Association Consortium (BCAC).

Abbreviation	Study	Country	Study design	Case definition	Control definition	Samples genotyped in iCOGS (1100delC carriers)	Additional BCAC samples (1100delC carriers)	Genotyped and included variants	Ref.
ABCFS	Australian Breast Cancer Family Study	Australia	Population-based case-control study	All cases diagnosed < age 40 plus a random sample of those diagnosed ages 40-59 from cancer registries in Victoria and New South Wales, plus a limited number diagnosed aged 60-69; cases living in Melbourne recruited from 1992-99 and in Sydney from 1993-98.	Identified from the electoral rolls in Melbourne from 1992-98 and Sydney from 1993-99. Frequency matched to cases by age in 5 year categories.	1240 (5)	710 (1)	77	1
ABCS	Amsterdam Breast Cancer Study	Netherlands	Hospital-based consecutive cases; population-based controls	All cases (operable, invasive mammacarcinoma) aged <50 and diagnosed from 1974-1994 in 4 Dutch hospitals.	Random women <50 years of age at baseline from 2 population-based prospective studies run by National Institute for Public Health and the Environment, The Netherlands.	736 (37) only cases	2,515 (69)	24	2
BBCC	Bavarian Breast Cancer Cases and Controls	Germany	Hospital based cases; population based controls	Consecutive, unselected cases with invasive breast cancer recruited at the University Breast Centre, Franconia in Northern Bavaria during 2002-2010.	Healthy women with no diagnosis of cancer aged 55 or older. Invited by a newspaper advertisement in Northern Bavaria, and recruited during 2002-2010.	8 (0) only cases	1,535 (13)	22	3,4
BBCS	British Breast Cancer Study	UK	Cancer registry and National Cancer Research network (NCRN) based cases; population based controls	1) English & Scottish Cancer Registries: all breast cancer cases who developed a first primary before age 65 in 1971 or later and who subsequently developed a second primary cancer. 2) Unilateral breast cancer cases diagnosed before age 70 in 1971 or later.	1) A friend, sister-in-law, daughter-in-law or other non-blood relative of cases. Recruitment of cases and controls began in January 2001.	222 (2) mostly controls	2,328 (25)	25	5,6
BIGGS	Breast Cancer in Galway Genetic Study	Ireland	Hospital based cases; population based controls	Unselected cases recruited from West of Ireland since 2001. Cases were recruited from University College Hospital Galway and surrounding hospitals	Women > 60 years with no personal history of any cancer and no family History of breast or ovarian cancer were identified from retirement groups in the West of Ireland (same catchment area as cases) during the period 2001-2008.	1,462 (3)	49 (0)	77	7,8
BSUCH	Breast Cancer Study of the University of Heidelberg	Germany	Hospital based cases; healthy blood donator controls	All cases diagnosed with breast cancer in 2007-2009 at the University Women`s Clinic Heidelberg	Healthy, unrelated, ethnically matched female blood donors recruited in 2007 & 2009 by German Red Cross Blood Service of Baden-Württemberg-Hessen, Institute of Transfusion Medicine & Immunology, Mannheim.	1,051 (12)	887 (7)	77	

CGPS	Copenhagen General Population Study	Denmark	Population-based	Consecutive, incident cases from 1 hospital with centralized care for a population of 400,000 women from 2001 to the present.	Community controls residing in the same region as cases and with no history of breast cancer were identified from the Copenhagen General Population Study recruited 2003-2007. All controls were known to still be breast cancer-free at the end of 2007.	1,953 (29) only cases	6,535 (44)	24	9,10
ESTHER	ESTHER Breast Cancer Study	Germany	Population-based case-control study	State-wide recruitment of breast cancer cases in all hospitals in Saarland/Germany in 2001-2003	State-wide recruitment of participants of a routine health check-up in Saarland/Germany in 2000-2002. A stratified random sample, matched to the cases by five year age groups, was selected as controls.	948 (5)	26 (0)	77	11
GC-HBOC	German Consortium for Hereditary Breast & Ovarian Cancer	Germany	Population-based familial case-control study	Index patients from German breast cancer families; BRCA1/2 mutation free, collected 1996-2007 via Institute of Human Genetics, University Heidelberg & Department of Gynaecology & Obstetrics, Cologne & Department of Gynaecology and Obstetrics at the Ludwig-Maximilians-University, Munich; Germany.	Healthy, unrelated, ethnically matched female blood donors recruited in 2004 & 2007 by German Red Cross Blood Service of Baden-Württemberg-Hessen, Institute of Transfusion Medicine & Immunology, Mannheim.	72 (0) only controls	1884 (20)	18	12,13
GENICA	Gene Environment Interaction and Breast Cancer in Germany	Germany	Population-based case-control study	Incident breast cancer cases enrolled between 2000 and 2004 from the Greater Bonn area (by of the hospitals within the study region); all enrolled within 6 months of diagnosis	Selected from population registries from 31 communities in the greater Bonn area; matched to cases in 5-year age classes between 2001 and 2004	889 (10)	1128 (8)	77	14,15
GESBC	Genetic Epidemiology Study of Breast Cancer by Age 50	Germany	Population-based study of women <50 years	All incident cases diagnosed <50 years of age in 1992-5 in two regions: Rhein-Neckar-Odenwald and Freiburg, by surveying the 38 clinics serving these regions	Selected from random lists of residents of the study regions supplied by population registries; two controls were selected for each case, matched by age and study region. Recruitment was carried out 1992-1998.		725 (2)	22	16
HABCS	Hannover Breast Cancer Study	Germany	Hospital-based case-control study	Cases who received radiotherapy for breast cancer at Hannover Medical School between 1997-2003, unselected for age or family history	Anonymous female blood bank donors at Hannover Medical School, collected from 8/2005-12/2005, with known age and ethnic background		2,037 (27)	23	17
HEBCS	Helsinki Breast Cancer Study	Finland	Hospital-based case-control study + additional familial cases	1) Consecutive cases (883) from the Department of Oncology, Helsinki University Central Hospital 1997-8 and 2000 2) Consecutive cases (986) from the Department of Surgery, Helsinki University Central Hospital 2001 – 2004 3) Familial breast cancer patients (536) from the Helsinki University Central Hospital, Departments of Oncology and Clinical Genetics (1995-)	Healthy females from the same geographical region in Southern Finland in 2003.	2,549 (62)	748 (33)	77	18-20

HMBCS	Hannover-Minsk Breast Cancer Study	Belarus	Hospital based cases; population based controls	Ascertainment at the Byelorussian Institute for Oncology and Medical Radiology Aleksandrov N.N. in Minsk or at one of 5 regional oncology centres in Gomel, Mogilev, Grodno, Brest or Vitebsk through the years 2002-2008.	Controls from the same population aged 18-72 years. Healthy female probands recruited from the same geographical regions as cases during the years 2002-2008. About 75% of controls were women invited for general medical examination at five regional gynaecology clinics and cancer-free volunteers ascertained at the Institute for Inherited Diseases in Minsk; 20% were cancer-free female blood bank donors recruited at Republic Blood Bank, Minsk, Belarus; finally 5% of controls were healthy cancer-free relatives of some breast cancer patients.	772 (4)	1,750 (10)	77	21
HUBCS	Hannover-Ufa Breast Cancer Study	Russia	Hospital based cases; population based controls	Consecutive Russian breast cancer patients aged 24-86 years ascertained at one of the two participating oncological centres in Bashkorstostan and Siberia through the years 2000-2008	Population controls aged 18-84 years recruited from a population study of different populations of Russia. Healthy volunteers (without any malignancy) were selected from the same geographical regions during the years 2002-2008.		2,394 (6)	18	21
KARBAC	Karolinska Breast Cancer Study	Sweden	Population and hospital-based cases; geographically matched controls	1. Familial cases from Department of Clinical Genetics, Karolinska University Hospital, Stockholm. 2. Consecutive cases from Department of Oncology, Huddinge & Söder Hospital, Stockholm 1998-2000	Blood donors of mixed gender from same geographical region. Excess material was received from all blood donors over a 3 month period in 2004 (approximately 3000) and DNA was extracted from a random sample of 1500	1,373 (12)	222 (4)	77	22,23
KBCP	Kuopio Breast Cancer Project	Finland	Population-based prospective clinical cohort	Women seen at Kuopio University Hospital between 1990 and 1995 because of breast lump, mammographic abnormality, or other breast symptom who were found to have breast cancer	Age and long-term area-of-residence matched controls selected from the National Population Register and interviewed in parallel with the cases	614 (12)	216 (5)	77	24,25
kConFab/ AOCS	Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study	Australia and New Zealand	Clinic-based recruitment of familial breast cancer patients (cases); population-based case-control study of ovarian cancer (controls only)	Cases were from multiple-case breast and breast-ovarian families recruited though family cancer clinics from across Australia and New Zealand from 1998 to the present. Cases were selected for inclusion in BCAC studies if (i) family was negative for mutations in BRCA1 and BRCA2 (ii) case was the index for the family, defined as youngest breast cancer affected family member.	Female controls were ascertained by the Australian Ovarian Cancer Study identified from the electoral rolls from all over Australia from 2002-2006.	1,145 (12)	160 (0)	77	26,27

LMBC	Leuven Multidisciplinary Breast Centre	Belgium	Hospital-based case-control study	All patients diagnosed with breast cancer and seen in the Multidisciplinary Breast Centre in Leuven (Gashuisberg) since June 2007 plus retrospective collection of cases diagnosed since 2000	Healthy controls (blood donors) collected at the Red Cross and located in Gasthuisberg hospital (Oct-2007-March 2008)	1,609 (12)	87 (1)	77	28,29
MCBCS	Mayo Clinic Breast Cancer Study	USA	Hospital-based case-control study	Incident cases residing in 6 states (MN, WI, IA, IL, ND, SD) seen at the Mayo Clinic in Rochester, MN from 2002-5	Women without cancer presenting for general medical examination at the Mayo Clinic. Controls were recruited concurrently with cases and were frequency matched to cases on age, ethnicity and county/state	1,663 (15)	524 (6)	77	30
MCCS	Melbourne Collaborative Cohort Study	Australia	Population-based prospective cohort study	Incident cases diagnosed within the Melbourne Collaborative Cohort Study during the follow-up from baseline (1990-1994) to 2008 of the 24469 participating women	Random sample of the initial cohort	538 (4)	479 (3)	77	31
NBCS	Norwegian Breast Cancer Study	Norway	Hospital-based case-control study	Incidence cases from three different hospitals: 1) Cases (114) mean age 64 (28-92) at Ullevål Univ. Hospital 1990-94 2) cases (182) mean age 59 (26-75) referred to Norwegian Radium Hospital 1975-1986 3) cases (124), mean age 56 (29-82)) with stage I or II disease, in the Oslo micro-metastases study at Norwegian Radium Hospital between 1995-1998, 4) cases (71) mean age 67 (37–82) with locally advanced disease at Haukeland Univ. Hospital.	Control subjects were healthy women, age 55-71, residing in Tromsø (440), and Bergen (109) attending the Norwegian Breast Cancer Screening Program.	81 (0)	2,453 (12)	17	32
NC-BCFR	Northern California Breast Cancer Family Registry	USA	Population-based familial case-control study	Cases included those enrolled in the NC-BCFR as part of Phase I and II recruitment. Incident cases aged <65 years diagnosed between 1995 and 2003 were identified through the SEER cancer registry of the Greater San Francisco Bay Area. All cases likely at increased genetic risk were eligible to enrol in the BCFR (dx at age <35 yrs, personal history of ovarian or childhood cancer, bilateral breast cancer with 1st dx at age <50, family history of breast or ovarian cancer in first-degree relatives). Cases not meeting these criteria were randomly sampled (2.5% of whites, 30% of African Americans, 28% of Hispanics, 38% of Asian Americans).	Controls were identified through random digit dialling conducted from 1999-2000 in the same geographic region. Controls were frequency matched to cases on 5-year age group and race/ethnicity, at a ratio of 1 control per 2 cases.		421 (7)	24	33

OFBCR	Ontario Familial Breast Cancer Registry	Canada	Population-based familial case-control study	Invasive cases (all aged 20-54 years and a random sample aged 55-69 years) were identified from the Ontario Cancer Registry 1996-1998. All those at high genetic risk (family history of specific cancers particularly breast and ovarian, early onset disease, Ashkenazi ethnicity or a diagnosis of multiple breast cancer) were eligible. Random samples of women not meeting these criteria were also asked to participate. During 2001-2005, some enrolment continued, but was limited to minority and high-risk families.	Unrelated, unaffected population controls were recruited between 2003-2005 by calling randomly selected residential telephone numbers throughout the same geographical region. Eligible controls were women with no history of breast cancer and were frequency-matched by 5-year age group to the expected age distribution of cases. Approximately, 65% of identified eligible women returned questionnaires, and 63% of these donated a blood specimen.	1,345 (11)	103 (0)	77	33
ORIGO	Leiden University Medical Centre Breast Cancer Study	Netherlands	Hospital-based prospective cohort study	Consecutive cases diagnosed 1996-2006 in 2 hospitals of South-West Netherlands (Leiden & Rotterdam). No selection for family history; Rotterdam cases selected for diagnosis aged <70. Cases with in situ carcinomas eligible.	Three groups of controls: 1) Blood bank healthy donors from Southwest Netherlands recruited in 1996, 2000 or 2007 2) People who married a person who was part of a family with high breast cancer risk (BRCA1/2/x). From the Southwest of the Netherlands, recruited 1990-1996 3) Females tested at the local clinical genetics department for familial diseases, excluding familial cancer syndromes (no mutation found in gene(s) related to the disease being tested), recruited 1995-2007.	178 (6) only cases	449 (17)	10	34,35
PBCS	NCI Polish Breast Cancer Study	Poland	Population-based case-control study	Incident cases from 2000-2003 identified through a rapid identification system in participating hospitals covering ~ 90% of all eligible cases, and cancer registries in Warsaw and Łódź covering 100% of all eligible cases	Randomly selected from population lists of all residents of Poland, stratified and frequency matched to cases by case city and age in 5 year categories. Recruited 2000-2003.	934 (6)	3,175 (10)	77	36
RBCS	Rotterdam Breast Cancer Study	Netherlands	Hospital based case-control study, Rotterdam area	Familial breast cancer patients selected from the clinical genetics centre at Erasmus Medical Centre; recruited 1994 - 2005	Spouses or mutation-negative siblings of heterozygous Cystic Fibrosis mutation carriers selected from the clinical genetics centre at Erasmus Medical Centre; recruited 1996 - 2006	1,313 (54)	118 (2)	77	37
SASBAC	Singapore and Sweden Breast Cancer Study	Sweden	Population-based case-control study	Incident cases from October 1993 to March 1995 identified via the 6 regional cancer registries in Sweden, to which reporting is mandatory.	Controls were randomly selected from the total population registry in 5-year age groups to match the expected age-frequency distribution among cases. Patients and controls were recruited from Oct 1993 through April 1995.	2,424 (20)	69 (1)	77	38

SBCS	Sheffield Breast Cancer Study	UK	Hospital-based case-control study	Women with pathologically confirmed breast cancer recruited from surgical outpatient clinics at the Royal Hallamshire Hospital, Sheffield, 1998 – 2005; cases are a mixture of prevalent and incident disease	Unselected women attending the Sheffield Mammography Screening Service between Sep 2000 - Aug 2004, if their mammograms showed no evidence of a breast lesion	1,536 (13)	273 (1)	77	39,40
SEARCH	Study of Epidemiology and Risk factors in Cancer Heredity	UK	Population-based case-control study	2 groups of cases identified through East Anglian Cancer Registry: 1) prevalent cases diagnosed 1991-1996 under 55 years of age at diagnosis, recruited 1996-2002 2) incident cases diagnosed since 1996 under 70 years of age at diagnosis, recruited 1996-present.	Two groups of controls: 1) selected from the EPIC-Norfolk cohort study of 25,000 individuals age 45-74 recruited between 1992 and1994, based in the same geographic region as cases 2) selected from GP practices from March 2003 to present, frequency matched to cases by age and geographic region	11,874 (110)	765 (10)	77	41
UCIBCS	UCI Breast Cancer Study	USA	Population-based case-control study	All cases diagnosed in Orange County, California, during one-year period beginning March 1, 1994. Ascertained through the population-based Cancer Surveillance Program of Orange County California (CSPOC)	Female controls under age 75 years without history of cancer recruited using random digit dialing among Orange County residents & frequency matched to cases by age & race/ethnicity. Recruited from 1998-2003		1,287 (10)	23	42,43
UKBGS	UK Breakthrough Generations Study	UK	Prospective cohort study: nested case-control study of women who had had breast cancer prior to entry into the cohort	All members who had had breast cancer before entry into the Breakthrough Generations Study (cohort of 100,000+ women followed up for breast cancer, recruited from the UK during 2003-2009).	Women who had not had breast cancer before entry into the cohort study, 1:1 matched to cases on date of birth, year of entry into the study (2003-2009), source of recruitment, blood sample and ethnicity	20 (0)	4,601 (38)	22	

Note: Genotype data was included from individual studies on a per locus basis. Genotype data from each study and each variant was included in the analyses, if the study provided genotype data from at least one invasive breast cancer patients carrying CHEK2*1100delC.

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Table S2. CHEK2*1100delC genotype data availability for breast cancer (BC) cases and controls.

	All BC cases	1100delC BC cases	All controls	1100delC controls	All subjects	1100delC subjects
iCOGS subjects[a]	21,375	368	17,174	88	38,549	456
Additional BCAC subjects[a]	17,764	256	22,889	136	40,653	392
Total number of subjects[a]	39,139	624	40,063	224	79,202	848
Subjects with complete data[b]	17,640	285	15,984	84	33,624	369

[a] Data for pairwise interaction analyses was included on a per variant basis and came from two sources: iCOGS genotyping array (data on 76 variants) and earlier BCAC studies (data on 25 variants).

[b] For all analyses involving the polygenic risk score, only study subjects with complete quality controlled data on all 76 variants were included. Complete data was available from altogether 33,624 study subjects.

Table S3. Description of genotype data coverage and genotyping methods for each low penetrance variant.

Variant	Number of samples from iCOGS[1-3]	Number of additional BCAC samples	Genotyping methods for additional BCAC samples
[a]**rs1045485 / rs17468277**	38,435	31,218	rs1045485: TaqMan, Sequenom iPLEX, illumina, Amplifluor, SNPstream, RFLP, MALDI-TOF MS, ARMS rs17468277: TaqMan, Sequenom MassArray and iPLEX[4]
[a]**rs999737 / rs10483813**	38,217	34,769	rs999737: TaqMan, Sequenom MassArray and iPLEX rs10483813: TaqMan, Sequenom MassArray and iPLEX[5]
rs10069690	35,258		
rs1011970	38,363	34,201	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[6]
rs10472076	35,273		
rs10759243	35,269		
rs10771399	38,348	30,917	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[7]
rs10941679	38,210	38,587	TaqMan, Sequenom MassArray and iPLEX[8]
rs10995190	38,367	34,824	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[6]
rs11075995	35,269		
rs11199914	35,275		
rs11242675	35,254		
rs11249433	38,212	34,811	TaqMan, Sequenom MassArray and iPLEX[5]
rs11552449	35,276		
rs11571833	35,279		
rs11780156	35,271		
rs11814448	35,279		
rs11820646	35,274		
rs12422552	35,273		
rs12493607	35,268		
rs12662670	38,548	20,180	TaqMan, Sequenom MassArray and iPLEX[9]
rs12710696	35,274		
rs1292011	37,618	28,903	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[7]
rs132390	35,278		
rs13281615	37,562	23,553	TaqMan, Sequenom MassArray and iPLEX[10]
rs13329835	35,277		
rs13387042	38,449	35,998	TaqMan, Sequenom MassArray and iPLEX[11]
rs1353747	35,279		
rs1432679	35,221		
rs1436904	35,268		
rs1550623	35,262		
rs16857609	35,269		
rs17356907	35,244		
rs17529111	35,270		
rs17817449	35,275		
rs2016394	35,132		
rs204247	35,275		
rs2046210	38,183	28,722	TaqMan, Sequenom MassArray and iPLEX[9]
rs2236007	35,272		
rs2363956	37,301	15,997	TaqMan, Sequenom MassArray and iPLEX[12]
rs2380205	38,366	34,234	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[6]
rs2588809	35,276		
rs2736108	35,260		
rs2823093	38,368	34,004	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[7]
rs2943559	34,977		
rs2981579	35,277		
rs2981582	38,543	35,382	TaqMan, Sequenom MassArray and iPLEX[10]
rs3757318	38,547		
rs3760982	35,243		
rs3803662	38,463	28,204	TaqMan, Sequenom MassArray and iPLEX[10]
rs3817198	38,373	27,067	TaqMan, Sequenom MassArray and iPLEX[10]
rs3903072	35,266		
rs4245739	35,276		
rs4808801	35,255		

rs4849887	35,277		
rs4973768	38,395	34,683	TaqMan, Sequenom MassArray and iPLEX[13]
rs527616	35,279		
rs554219	35,269		
rs6001930	35,279		
rs614367	36,413	26,730	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[6]
rs616488	35,271		
rs6472903	35,223		
rs6504950	38,467	36,006	TaqMan, Sequenom MassArray and iPLEX[12]
rs6678914	35,275		
rs6762644	35,268		
rs6828523	35,267		
rs704010	38,356	34,720	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[6]
rs7072776	35,277		
rs720475	35,278		
rs75915166	35,276		
rs7904519	35,251		
rs8170	38,358	29,359	TaqMan, Sequenom MassArray and iPLEX[12]
rs865686	38,364	30,866	TaqMan, Sequenom MassArray and iPLEX, Fluidigm[14]
rs889312	38,466	29,822	TaqMan, Sequenom MassArray and iPLEX[10]
rs941764	35,242		
rs9693444	35,277		
rs9790517	35,271		

[a] Genotype data of linked variants (r^2=1) were combined for all analyses.

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Table S4. Odds ratios (OR) and 95% confidence intervals (CI) estimated for the whole dataset and for the carriers of CHEK2*1100delC, as well as for pairwise interaction between each variant and CHEK2*1100delC for (a) breast cancer (b) estrogen receptor positive (ER+) breast cancer.

a]

	major: minor	ALL		1100delC carriers		Interaction		Likelihood ratio test	
		OR	95% CI	OR	95% CI	OR	95% CI	p-value	corrected p-value[a]
rs1045485/rs17468277		0.95	[0.92 - 0.97]	0.98	[0.66 - 1.45]	0.96	[0.67 - 1.39]	0.84	0.98
rs999737/rs10483813		0.92	[0.90 - 0.94]	0.72	[0.53 - 0.99]	0.77	[0.58 - 1.03]	0.079	0.61
rs10069690	C:T	1.04	[1.01 - 1.07]	0.99	[0.64 - 1.53]	0.99	[0.65 - 1.49]	0.95	0.98
rs1011970	G:T	1.07	[1.04 - 1.09]	1.17	[0.81 - 1.68]	1.02	[0.73 - 1.43]	0.88	0.98
rs10472076	T:C	1.06	[1.03 - 1.09]	0.73	[0.50 - 1.08]	0.73	[0.50 - 1.05]	0.093	0.65
rs10759243	C:A	1.07	[1.03 - 1.10]	1.11	[0.74 - 1.68]	1.06	[0.72 - 1.56]	0.77	0.98
rs10771399	A:G	0.84	[0.81 - 0.86]	0.72	[0.48 - 1.08]	0.77	[0.53 - 1.12]	0.18	0.96
rs10941679	A:G	1.12	[1.10 - 1.15]	1.27	[0.94 - 1.72]	1.14	[0.87 - 1.51]	0.34	0.97
rs10995190	G:A	0.88	[0.86 - 0.90]	0.90	[0.63 - 1.29]	1.10	[0.79 - 1.53]	0.59	0.98
rs11075995	A:T	1.06	[1.03 - 1.10]	1.67	[1.04 - 2.69]	1.52	[0.98 - 2.36]	0.057	0.61
rs11199914	C:T	0.95	[0.93 - 0.98]	1.23	[0.82 - 1.86]	1.19	[0.81 - 1.75]	0.38	0.97
rs11242675	T:C	0.97	[0.94 - 1.00]	0.80	[0.55 - 1.16]	0.81	[0.57 - 1.15]	0.24	0.96
rs11249433	**A:G**	**1.12**	**[1.10 - 1.14]**	**0.80**	**[0.62 - 1.03]**	**0.74**	**[0.59 - 0.94]**	**0.014**	**0.54**
rs11552449	C:T	1.08	[1.05 - 1.12]	1.43	[0.86 - 2.37]	1.23	[0.77 - 1.97]	0.38	0.97
rs11571833	A:T	1.28	[1.11 - 1.47]	1.75	[0.20 - 15.63]	1.38	[0.17 - 11.47]	0.76	0.98
rs11780156	**G:A**	**1.09**	**[1.05 - 1.13]**	**2.16**	**[1.21 - 3.88]**	**1.86**	**[1.07 - 3.22]**	**0.021**	**0.54**
rs11814448	A:C	1.26	[1.14 - 1.38]	0.52	[0.16 - 1.71]	0.48	[0.16 - 1.47]	0.22	0.96
rs11820646	C:T	0.94	[0.91 - 0.97]	0.87	[0.60 - 1.26]	0.93	[0.66 - 1.30]	0.66	0.98
rs12422552	G:C	1.06	[1.02 - 1.09]	1.29	[0.85 - 1.95]	1.25	[0.85 - 1.85]	0.25	0.96
rs12493607	G:C	1.06	[1.03 - 1.09]	0.97	[0.66 - 1.42]	0.98	[0.69 - 1.40]	0.92	0.98
rs12662670	A:C	1.14	[1.10 - 1.18]	1.36	[0.73 - 2.56]	1.26	[0.70 - 2.25]	0.44	0.97
rs12710696	C:T	1.05	[1.02 - 1.08]	0.96	[0.66 - 1.41]	0.92	[0.64 - 1.32]	0.64	0.98
rs1292011	A:G	0.93	[0.91 - 0.95]	1.01	[0.75 - 1.35]	1.05	[0.80 - 1.37]	0.73	0.98
rs132390	T:C	1.18	[1.10 - 1.27]	0.96	[0.57 - 1.62]	0.91	[0.56 - 1.46]	0.69	0.98
rs13281615	A:G	1.11	[1.09 - 1.14]	0.85	[0.63 - 1.13]	0.80	[0.61 - 1.05]	0.11	0.65
rs13329835	A:G	1.07	[1.04 - 1.11]	1.14	[0.73 - 1.79]	1.23	[0.81 - 1.88]	0.33	0.97
rs13387042	A:G	1.13	[1.11 - 1.15]	1.12	[0.87 - 1.44]	0.96	[0.76 - 1.21]	0.71	0.98
rs1353747	T:G	0.89	[0.85 - 0.93]	1.09	[0.51 - 2.35]	1.34	[0.66 - 2.75]	0.41	0.97
rs1432679	T:C	1.10	[1.07 - 1.13]	1.12	[0.75 - 1.66]	0.93	[0.65 - 1.34]	0.70	0.98
rs1436904	T:G	0.97	[0.94 - 1.00]	1.17	[0.79 - 1.71]	1.16	[0.80 - 1.67]	0.44	0.97
rs1550623	A:G	0.94	[0.91 - 0.98]	0.85	[0.51 - 1.41]	0.93	[0.58 - 1.49]	0.76	0.98
rs16857609	C:T	1.08	[1.05 - 1.11]	1.30	[0.84 - 2.01]	1.19	[0.80 - 1.78]	0.39	0.97
rs17356907	A:G	0.91	[0.88 - 0.93]	0.83	[0.55 - 1.25]	1.00	[0.68 - 1.47]	1.00	1.00
rs17529111	T:C	1.07	[1.03 - 1.10]	1.14	[0.73 - 1.78]	1.09	[0.71 - 1.67]	0.69	0.98
rs17817449	T:G	0.93	[0.91 - 0.96]	0.89	[0.61 - 1.29]	0.95	[0.67 - 1.35]	0.77	0.98
rs2016394	G:A	0.95	[0.92 - 0.97]	1.05	[0.74 - 1.48]	1.07	[0.77 - 1.48]	0.70	0.98
rs204247	**A:G**	**1.05**	**[1.02 - 1.08]**	**0.70**	**[0.49 - 1.00]**	**0.64**	**[0.46 - 0.89]**	**0.007**	**0.54**
rs2046210	G:A	1.09	[1.07 - 1.12]	1.04	[0.77 - 1.39]	0.95	[0.72 - 1.24]	0.69	0.98
rs2236007	G:A	0.93	[0.89 - 0.96]	1.20	[0.77 - 1.88]	1.10	[0.74 - 1.65]	0.64	0.98
rs2363956	A:C	0.98	[0.95 - 1.00]	1.26	[0.92 - 1.73]	1.29	[0.97 - 1.71]	0.074	0.61
rs2380205	C:T	0.98	[0.96 - 1.00]	1.02	[0.79 - 1.33]	1.03	[0.81 - 1.30]	0.82	0.98
rs2588809	C:T	1.07	[1.03 - 1.11]	1.13	[0.65 - 1.95]	1.26	[0.75 - 2.13]	0.37	0.97
rs2736108	C:T	0.93	[0.91 - 0.96]	0.95	[0.64 - 1.43]	1.04	[0.71 - 1.53]	0.83	0.98
rs2823093	G:A	0.93	[0.91 - 0.95]	0.83	[0.62 - 1.12]	0.85	[0.65 - 1.12]	0.25	0.96
rs2943559	A:G	1.14	[1.09 - 1.21]	1.30	[0.62 - 2.71]	1.17	[0.59 - 2.32]	0.64	0.98
rs2981579	G:A	1.25	[1.22 - 1.29]	1.40	[0.95 - 2.04]	1.02	[0.71 - 1.45]	0.92	0.98
rs2981582	**G:A**	**1.26**	**[1.23 - 1.28]**	**1.68**	**[1.28 - 2.20]**	**1.29**	**[1.00 - 1.67]**	**0.044**	**0.61**
rs3757318	G:A	1.15	[1.10 - 1.20]	1.71	[0.66 - 4.42]	1.55	[0.63 - 3.82]	0.31	0.97
rs3760982	G:A	1.06	[1.03 - 1.09]	1.19	[0.83 - 1.71]	1.10	[0.78 - 1.55]	0.59	0.98
rs3803662	G:A	1.24	[1.22 - 1.27]	1.17	[0.87 - 1.56]	1.01	[0.77 - 1.33]	0.93	0.98
rs3817198	T:C	1.06	[1.04 - 1.09]	1.12	[0.84 - 1.50]	0.98	[0.75 - 1.28]	0.89	0.98
rs3903072	G:T	0.94	[0.92 - 0.97]	0.97	[0.66 - 1.41]	0.94	[0.66 - 1.33]	0.72	0.98

rs4245739	A:C	1.03	[1.00 - 1.06]	1.06	[0.66 - 1.69]	1.05	[0.68 - 1.63]	0.81	0.98
rs4808801	A:G	0.92	[0.89 - 0.95]	0.65	[0.44 - 0.96]	0.72	[0.50 - 1.02]	0.067	0.61
rs4849887	C:T	0.92	[0.88 - 0.97]	1.00	[0.52 - 1.95]	1.04	[0.56 - 1.94]	0.90	0.98
rs4973768	C:T	1.09	[1.07 - 1.11]	1.13	[0.87 - 1.47]	0.98	[0.77 - 1.24]	0.88	0.98
rs527616	G:C	0.95	[0.92 - 0.97]	1.04	[0.71 - 1.53]	1.20	[0.84 - 1.70]	0.32	0.97
rs554219	C:G	1.26	[1.21 - 1.32]	1.21	[0.67 - 2.19]	0.99	[0.56 - 1.75]	0.98	0.99
rs6001930	T:C	1.12	[1.08 - 1.17]	0.84	[0.50 - 1.40]	0.74	[0.45 - 1.19]	0.22	0.96
rs614367	C:T	1.20	[1.17 - 1.24]	1.28	[0.86 - 1.89]	1.02	[0.70 - 1.49]	0.91	0.98
rs616488	A:G	0.94	[0.91 - 0.97]	0.92	[0.61 - 1.39]	1.05	[0.72 - 1.54]	0.80	0.98
rs6472903	T:G	0.92	[0.89 - 0.95]	0.78	[0.48 - 1.26]	0.79	[0.51 - 1.23]	0.30	0.97
rs6504950	G:A	0.93	[0.91 - 0.95]	1.01	[0.76 - 1.36]	1.09	[0.83 - 1.42]	0.54	0.98
rs6678914	G:A	0.98	[0.95 - 1.00]	1.14	[0.78 - 1.67]	1.15	[0.81 - 1.64]	0.44	0.97
rs6762644	A:G	1.06	[1.03 - 1.09]	1.09	[0.75 - 1.60]	0.94	[0.67 - 1.32]	0.71	0.98
rs6828523	C:A	0.89	[0.86 - 0.93]	0.77	[0.43 - 1.40]	0.87	[0.51 - 1.51]	0.63	0.98
rs704010	**C:T**	**1.07**	**[1.05 - 1.10]**	**0.85**	**[0.66 - 1.10]**	**0.78**	**[0.62 - 0.99]**	**0.042**	**0.61**
rs7072776	G:A	1.07	[1.04 - 1.10]	1.44	[0.92 - 2.25]	1.23	[0.82 - 1.85]	0.30	0.97
rs720475	G:A	0.92	[0.89 - 0.95]	0.71	[0.46 - 1.10]	0.78	[0.53 - 1.16]	0.22	0.96
rs75915166	C:A	1.34	[1.26 - 1.41]	1.97	[0.77 - 5.05]	1.54	[0.62 - 3.79]	0.33	0.97
rs7904519	A:G	1.07	[1.04 - 1.10]	1.15	[0.80 - 1.66]	1.09	[0.78 - 1.54]	0.61	0.98
rs8170	G:A	1.03	[1.00 - 1.05]	0.82	[0.59 - 1.13]	0.78	[0.58 - 1.06]	0.11	0.65
rs865686	T:G	0.89	[0.87 - 0.90]	0.83	[0.64 - 1.10]	0.97	[0.76 - 1.25]	0.82	0.98
rs889312	A:C	1.10	[1.08 - 1.13]	0.92	[0.69 - 1.22]	0.79	[0.61 - 1.02]	0.073	0.61
rs941764	A:G	1.05	[1.02 - 1.09]	0.94	[0.65 - 1.36]	0.99	[0.70 - 1.40]	0.94	0.98
rs9693444	C:A	1.06	[1.03 - 1.09]	1.24	[0.84 - 1.84]	1.08	[0.75 - 1.56]	0.67	0.98
rs9790517	C:T	1.04	[1.00 - 1.07]	0.93	[0.59 - 1.44]	0.92	[0.60 - 1.39]	0.68	0.98

b]

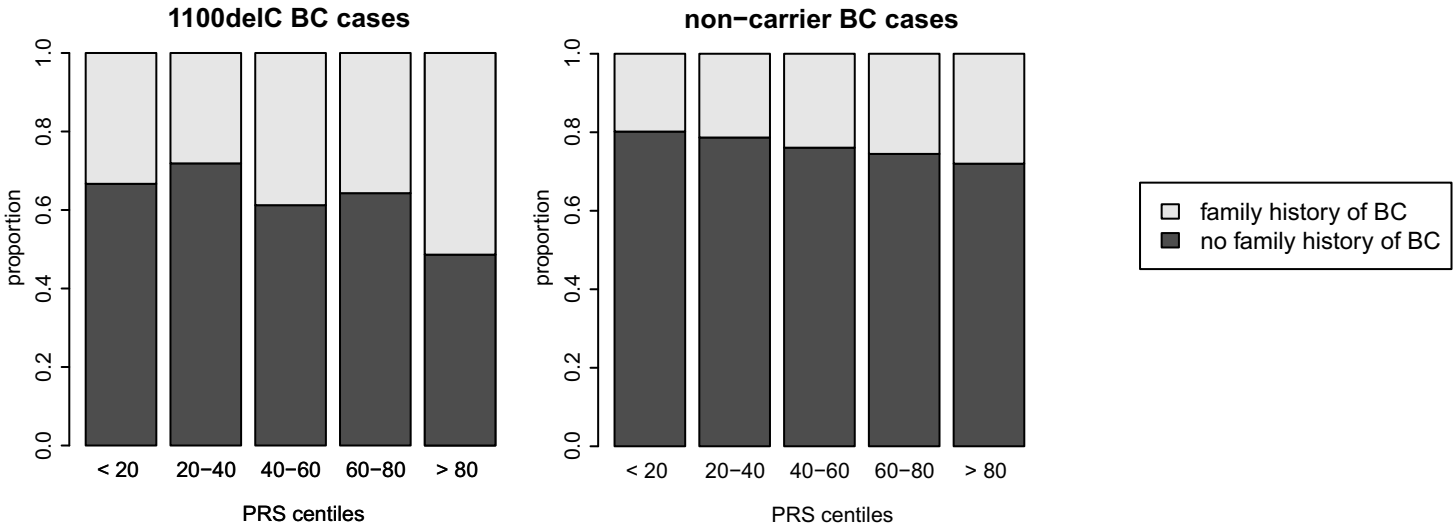
		ALL ER+		**ER+ 1100delC carriers**		**Interaction**		**Likelihood ratio test**	
	major: minor	OR	95% CI	OR	95% CI	OR	95% CI	p-value	corrected p-value[a]
rs1045485/rs17468277		0.96	[0.93 - 1.00]	1.18	[0.73 - 1.92]	1.02	[0.66 - 1.57]	0.94	0.99
rs999737/rs10483813		0.92	[0.89 - 0.95]	0.78	[0.54 - 1.15]	0.83	[0.59 - 1.17]	0.28	0.91
rs10069690	C:T	1.02	[0.99 - 1.06]	0.95	[0.59 - 1.53]	0.95	[0.61 - 1.47]	0.80	0.99
rs1011970	G:T	1.07	[1.03 - 1.10]	0.97	[0.63 - 1.51]	0.88	[0.60 - 1.29]	0.50	0.97
rs10472076	T:C	1.05	[1.02 - 1.09]	0.78	[0.51 - 1.19]	0.76	[0.51 - 1.11]	0.16	0.88
rs10759243	C:A	1.09	[1.05 - 1.12]	0.92	[0.59 - 1.45]	0.92	[0.62 - 1.38]	0.70	0.98
rs10771399	A:G	0.86	[0.82 - 0.89]	0.83	[0.51 - 1.34]	0.80	[0.51 - 1.24]	0.32	0.91
rs10941679	A:G	1.16	[1.13 - 1.19]	1.43	[1.00 - 2.04]	1.26	[0.91 - 1.73]	0.16	0.88
rs10995190	G:A	0.88	[0.85 - 0.91]	0.95	[0.61 - 1.46]	1.22	[0.83 - 1.81]	0.31	0.91
rs11075995	**A:T**	**1.04**	**[1.00 - 1.08]**	**1.65**	**[0.99 - 2.75]**	**1.59**	**[0.99 - 2.54]**	**0.047**	**0.46**
rs11199914	C:T	0.94	[0.91 - 0.97]	1.23	[0.78 - 1.93]	1.20	[0.80 - 1.82]	0.38	0.91
rs11242675	T:C	0.98	[0.95 - 1.01]	0.75	[0.49 - 1.13]	0.74	[0.51 - 1.07]	0.11	0.77
rs11249433	**A:G**	**1.14**	**[1.11 - 1.17]**	**0.71**	**[0.53 - 0.96]**	**0.67**	**[0.51 - 0.87]**	**0.0030**	**0.23**
rs11552449	C:T	1.10	[1.05 - 1.14]	1.42	[0.83 - 2.45]	1.24	[0.76 - 2.02]	0.38	0.91
rs11571833	A:T	1.34	[1.14 - 1.57]	1.93	[0.21 - 18.08]	1.22	[0.14 - 10.77]	0.86	0.99
rs11780156	**G:A**	**1.11**	**[1.06 - 1.15]**	**2.49**	**[1.31 - 4.73]**	**2.18**	**[1.21 - 3.92]**	**0.0060**	**0.23**
rs11814448	A:C	1.24	[1.11 - 1.38]	0.63	[0.18 - 2.23]	0.65	[0.20 - 2.07]	0.47	0.97
rs11820646	C:T	0.94	[0.91 - 0.97]	0.92	[0.62 - 1.38]	0.97	[0.67 - 1.39]	0.85	0.99
rs12422552	G:C	1.06	[1.02 - 1.10]	1.40	[0.89 - 2.20]	1.30	[0.85 - 1.97]	0.22	0.91
rs12493607	G:C	1.06	[1.03 - 1.10]	0.96	[0.64 - 1.45]	0.97	[0.67 - 1.40]	0.86	0.99
rs12662670	A:C	1.10	[1.05 - 1.15]	1.86	[0.88 - 3.90]	1.76	[0.89 - 3.48]	0.094	0.77
rs12710696	C:T	1.03	[1.00 - 1.06]	0.85	[0.56 - 1.30]	0.85	[0.58 - 1.26]	0.43	0.97
rs1292011	A:G	0.91	[0.88 - 0.93]	1.02	[0.71 - 1.47]	1.15	[0.84 - 1.57]	0.38	0.91
rs132390	T:C	1.17	[1.08 - 1.28]	1.10	[0.61 - 1.98]	0.99	[0.59 - 1.66]	0.98	0.99
rs13281615	**A:G**	**1.11**	**[1.08 - 1.14]**	**0.73**	**[0.52 - 1.00]**	**0.74**	**[0.55 - 1.00]**	**0.048**	**0.46**
rs13329835	A:G	1.08	[1.04 - 1.12]	1.18	[0.72 - 1.92]	1.24	[0.80 - 1.94]	0.33	0.91
rs13387042	A:G	1.14	[1.11 - 1.16]	1.35	[0.98 - 1.85]	1.05	[0.79 - 1.39]	0.74	0.99
rs1353747	T:G	0.90	[0.85 - 0.95]	1.08	[0.48 - 2.40]	1.44	[0.69 - 3.03]	0.32	0.91
rs1432679	T:C	1.10	[1.07 - 1.14]	1.00	[0.65 - 1.53]	0.91	[0.62 - 1.33]	0.62	0.97

rs1436904	T:G	0.96	[0.92 - 0.99]	1.03	[0.68 - 1.55]	1.06	[0.72 - 1.56]	0.78	0.99
rs1550623	A:G	0.95	[0.91 - 0.99]	0.89	[0.51 - 1.54]	1.06	[0.64 - 1.76]	0.83	0.99
rs16857609	C:T	1.09	[1.05 - 1.13]	1.45	[0.90 - 2.35]	1.30	[0.85 - 1.99]	0.22	0.91
rs17356907	A:G	0.90	[0.87 - 0.93]	0.79	[0.51 - 1.23]	0.97	[0.65 - 1.45]	0.89	0.99
rs17529111	T:C	1.06	[1.03 - 1.11]	1.17	[0.72 - 1.88]	1.10	[0.71 - 1.71]	0.66	0.98
rs17817449	T:G	0.93	[0.90 - 0.97]	0.83	[0.55 - 1.24]	0.95	[0.65 - 1.38]	0.77	0.99
rs2016394	G:A	0.94	[0.91 - 0.97]	1.05	[0.73 - 1.52]	1.12	[0.79 - 1.59]	0.51	0.97
rs204247	**A:G**	**1.06**	**[1.02 - 1.09]**	**0.85**	**[0.57 - 1.27]**	**0.67**	**[0.47 - 0.96]**	**0.030**	**0.46**
rs2046210	G:A	1.07	[1.04 - 1.09]	0.91	[0.65 - 1.26]	0.85	[0.63 - 1.14]	0.28	0.91
rs2236007	G:A	0.92	[0.88 - 0.95]	1.13	[0.69 - 1.84]	1.13	[0.73 - 1.76]	0.58	0.97
rs2363956	A:C	1.02	[0.99 - 1.04]	1.29	[0.89 - 1.86]	1.29	[0.94 - 1.78]	0.11	0.77
rs2380205	C:T	0.97	[0.94 - 0.99]	1.06	[0.77 - 1.45]	1.08	[0.82 - 1.43]	0.57	0.97
rs2588809	C:T	1.09	[1.05 - 1.14]	1.19	[0.66 - 2.14]	1.41	[0.81 - 2.45]	0.21	0.91
rs2736108	C:T	0.94	[0.90 - 0.97]	0.89	[0.57 - 1.40]	1.00	[0.66 - 1.51]	0.99	0.99
rs2823093	G:A	0.92	[0.89 - 0.95]	0.91	[0.64 - 1.30]	0.88	[0.63 - 1.21]	0.43	0.97
rs2943559	A:G	1.14	[1.08 - 1.21]	1.54	[0.69 - 3.43]	1.17	[0.57 - 2.38]	0.66	0.98
rs2981579	G:A	1.31	[1.27 - 1.35]	1.37	[0.91 - 2.07]	1.00	[0.69 - 1.45]	0.99	0.99
rs2981582	G:A	1.31	[1.28 - 1.35]	1.41	[1.02 - 1.94]	1.09	[0.81 - 1.46]	0.57	0.97
rs3757318	G:A	1.10	[1.04 - 1.16]	1.32	[0.49 - 3.58]	1.29	[0.51 - 3.26]	0.58	0.97
rs3760982	G:A	1.06	[1.03 - 1.10]	1.12	[0.75 - 1.67]	1.05	[0.73 - 1.50]	0.80	0.99
rs3803662	G:A	1.27	[1.24 - 1.30]	0.99	[0.71 - 1.38]	0.85	[0.63 - 1.15]	0.29	0.91
rs3817198	T:C	1.07	[1.05 - 1.10]	1.13	[0.81 - 1.58]	0.98	[0.72 - 1.33]	0.88	0.99
rs3903072	G:T	0.94	[0.91 - 0.97]	1.03	[0.67 - 1.57]	0.99	[0.68 - 1.45]	0.97	0.99
rs4245739	A:C	1.00	[0.96 - 1.03]	1.08	[0.66 - 1.78]	1.13	[0.72 - 1.78]	0.59	0.97
rs4808801	**A:G**	**0.92**	**[0.89 - 0.95]**	**0.58**	**[0.38 - 0.88]**	**0.67**	**[0.46 - 0.98]**	**0.040**	**0.46**
rs4849887	C:T	0.91	[0.86 - 0.96]	1.19	[0.59 - 2.42]	1.21	[0.63 - 2.33]	0.56	0.97
rs4973768	C:T	1.11	[1.08 - 1.13]	1.08	[0.79 - 1.48]	0.91	[0.69 - 1.19]	0.49	0.97
rs527616	G:C	0.96	[0.93 - 0.99]	1.13	[0.74 - 1.71]	1.20	[0.83 - 1.75]	0.33	0.91
rs554219	C:G	1.30	[1.25 - 1.36]	1.36	[0.72 - 2.57]	0.99	[0.55 - 1.77]	0.96	0.99
rs6001930	T:C	1.12	[1.06 - 1.17]	1.01	[0.58 - 1.76]	0.85	[0.51 - 1.42]	0.55	0.97
rs614367	C:T	1.25	[1.21 - 1.29]	1.35	[0.82 - 2.21]	0.97	[0.62 - 1.53]	0.91	0.99
rs616488	A:G	0.95	[0.92 - 0.98]	0.88	[0.56 - 1.38]	0.99	[0.65 - 1.49]	0.94	0.99
rs6472903	T:G	0.92	[0.89 - 0.96]	0.82	[0.48 - 1.39]	0.79	[0.49 - 1.26]	0.32	0.91
rs6504950	G:A	0.93	[0.90 - 0.95]	0.93	[0.66 - 1.31]	1.02	[0.75 - 1.39]	0.91	0.99
rs6678914	G:A	0.99	[0.96 - 1.02]	1.05	[0.69 - 1.60]	1.08	[0.74 - 1.59]	0.69	0.98
rs6762644	A:G	1.07	[1.04 - 1.11]	1.01	[0.67 - 1.53]	0.91	[0.63 - 1.32]	0.61	0.97
rs6828523	C:A	0.87	[0.83 - 0.91]	0.61	[0.32 - 1.18]	0.82	[0.46 - 1.46]	0.50	0.97
rs704010	**C:T**	**1.08**	**[1.06 - 1.11]**	**0.81**	**[0.59 - 1.11]**	**0.74**	**[0.55 - 0.98]**	**0.037**	**0.46**
rs7072776	G:A	1.08	[1.04 - 1.12]	1.46	[0.90 - 2.35]	1.21	[0.79 - 1.86]	0.38	0.91
rs720475	G:A	0.91	[0.88 - 0.95]	0.67	[0.42 - 1.07]	0.76	[0.50 - 1.16]	0.20	0.91
rs75915166	C:A	1.37	[1.28 - 1.45]	2.27	[0.84 - 6.09]	1.63	[0.64 - 4.15]	0.28	0.91
rs7904519	A:G	1.05	[1.02 - 1.09]	1.15	[0.78 - 1.71]	1.08	[0.75 - 1.55]	0.69	0.98
rs8170	G:A	0.99	[0.96 - 1.02]	0.76	[0.52 - 1.11]	0.77	[0.54 - 1.08]	0.13	0.83
rs865686	T:G	0.86	[0.84 - 0.88]	0.89	[0.64 - 1.23]	0.99	[0.74 - 1.32]	0.92	0.99
rs889312	**A:C**	**1.12**	**[1.09 - 1.15]**	**0.83**	**[0.59 - 1.16]**	**0.68**	**[0.50 - 0.92]**	**0.013**	**0.33**
rs941764	A:G	1.06	[1.03 - 1.10]	0.86	[0.57 - 1.29]	0.88	[0.61 - 1.28]	0.50	0.97
rs9693444	C:A	1.07	[1.03 - 1.10]	1.24	[0.81 - 1.88]	1.09	[0.75 - 1.61]	0.64	0.98
rs9790517	C:T	1.04	[1.00 - 1.08]	0.93	[0.57 - 1.51]	0.93	[0.60 - 1.46]	0.77	0.99

[a] The p-values from likelihood ratio tests have been corrected for multiple testing using the Benjamini-Hochberg method.

Note: Results in bold indicate pairwise interactions with nominal significance.

Figure S1. Relationship between the polygenic risk score (PRS) and positive family history of breast cancer.



Odds ratio for family history per unit standard deviation of PRS 1.29 [1.01-1.65].

Odds ratio for family history per unit standard deviation of PRS 1.17 [1.12-1.21].